Advanced Pharmaceutical Technology

Nanotechnology in Drug Delivery

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Introduction

- Nanotechnology

  "The design, characterization, and production of materials that have one or more dimension between 1 – 100 nm"

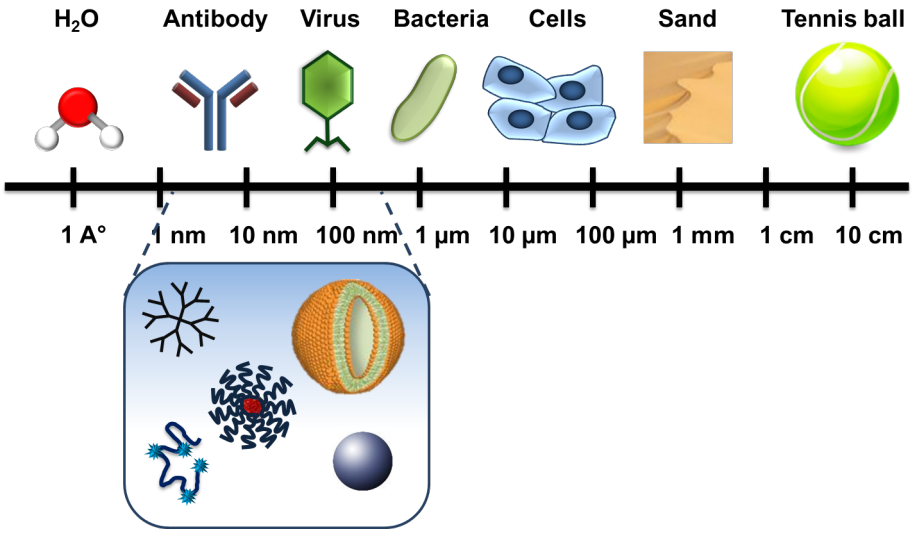
  – Size range is debatable
    - e.g. FDA sets the upper limit as 1000 nm
- Nanomedicine

  "The medical application of nanotechnology"

Introduction

- The general definition can encompass many systems
  - Macromolecules e.g. antibodies
  - Nanoparticles
  - Polymer-drug and polymer-protein conjugates
  - Liposomes
- The dimensions of the material can influence its function
  - Bioavailability
  - Toxicity
  - Potency

Introduction



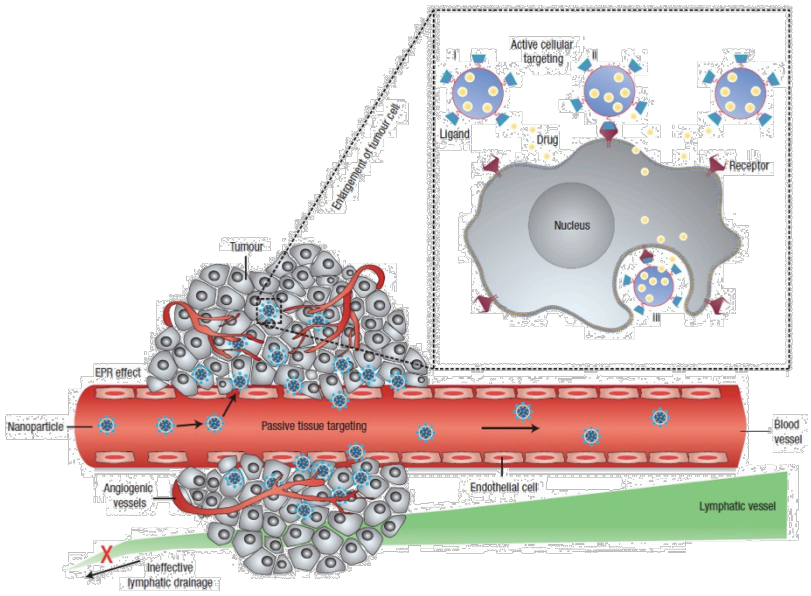
Pharmaceutical advantages of nanotechnology

1. Enhanced solubility and dissolution
   - High surface area to volume ratio → increased dissolution rate of drugs
2. Enhanced drug delivery
   - Prolonging drug residence time in the systemic circulation
   - Enable drug targeting and transport across biological barriers

Targeted drug delivery

- One of the most important advantages of nanotechnology is the ability to target drugs to specific organs, tissues, or cells
- Targeting can be achieved through two main mechanisms: active and passive targeting

Targeted drug delivery



Passive targeting

- Accumulation of the nanocarrier in a tissue due to the **enhanced permeability and retention (EPR)** effect
- Normal state: endothelial lining of blood vessels is continuous and tight junctions prevent the passage of large particles
- Disease state (inflammation, tumors): the integrity of blood vessels is compromised resulting in “gaps” in the endothelial lining ~300 nm in size **(enhanced permeability)**

Passive targeting

- In case of tumors, their rapid growth generates new blood vessels (angiogenesis) that do not have time to mature and develop the tight junctions
- This is also combined with an impaired lymphatic drainage system **(enhanced retention)**
- Some types of nanocarriers (200 – 500 nm) are too large to cross intact blood vessels, but can accumulate at the disease site due to the EPR effect → better drug action and less side effects

Active targeting

- Achieved by decorating the surface of the nanocarrier with targeting moieties (ligands)
- Relies on the specific interaction between the targeting ligand and a receptor unique to the disease site
- e.g. antibodies, folic acid (folate receptors are overexpressed by some types of tumors)

Nanotechnology in anti-cancer therapy

- Nanotechnology-based medicines have been widely explored in anti-cancer therapy due to their targeting ability
- This has resulted in enhancing the therapeutic efficacy and reducing the systemic side effects of many anti-cancer drugs (e.g. paclitaxel, doxorubicin, methotrexate, …)

Key properties of anti-cancer nanomedicines

- Nanocarrier size
- Surface properties
- Presence of targeting ligands

Nanocarrier size

- The size range is highly debatable (10 – 100 nm, 50 – 200 nm, …)
- It is estimated that the renal elimination threshold is 10 nm
- The upper size limit can vary significantly even within the same patient
- Particles within this range will be capable of achieving passive targeting through the EPR effect
- However, these particles can still accumulate in the liver

Surface properties

- Surface properties can have a crucial effect on nanocarrier behavior due to the high surface-to-volume ratio
- The ultimate fate of nanocarriers within the body is dependent on a combination of size and surface properties
- Most important surface properties: steric stabilization and surface charge

Surface properties

- Steric stability:
  - Hydrophilic nonionic polymers such as polyethylene glycol (PEG) can form a highly hydrated layer when attached to the surface of the nanocarrier
  - This hydrated layer prevents particle aggregation by producing strong repulsion
  - It has also been found to prevent immune recognition by hiding the nanocarrier behind a water layer
  - As a result, these “stealth” nanocarriers are generally associated with prolonged circulation times

Surface properties

- Surface charge:
  - Nanocarriers that are slightly negative or slightly positive have minimal self–self and self–non-self interactions
  - Negatively charged particles are repelled by cell surfaces and the inside surface of blood vessels
  - As the surface charge becomes larger (positive or negative), macrophage clearance is increased
  - Thus, unwanted nanocarrier uptake by the immune system can be prevented by steric stabilization and minimizing electrostatic interactions

Targeting ligands

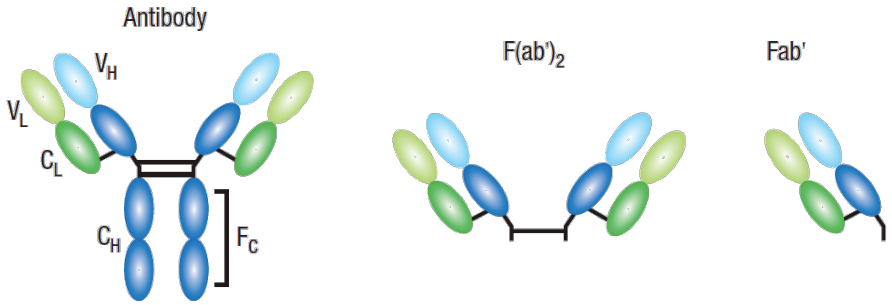
- Tissue-specificity can be greatly enhanced by decorating the nanocarrier surface with targeting moieties
- It is generally known that higher binding affinity increases targeting efficacy
- However, high binding affinity can sometimes decrease nanoparticle penetration
- Multivalent binding (simultaneous binding of multiple ligands to multiple receptors) may also be used to improve targeting

Type of targeting ligands

- Proteins (mainly antibodies and their fragments)
- Nucleic acids (aptamers)
- Others (peptides, vitamins, carbohydrates)

Monoclonal antibodies (mAbs)

- Targeting cancer with a mAb was first described in 1981
- Many have been approved since then
- Used as the whole antibody or just the Fab fraction

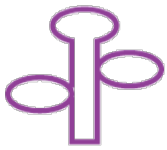


Examples of licensed mAbs or Fabs

Brand name	Generic name	Description
Avastin®	Bevacizumab	IgG against VEGF-A to block angiogenesis
Herceptin®	Trastuzumab	IgG against HER-2 to block tumor cell growth and mark it for destruction
Humira®	Adalimumab	IgG against TNF-α to downregulate inflammatory reactions

Aptamers

- Aptamers are short single-stranded DNA or RNA oligonucleotides selected in vitro from a large number of random sequences
- They are selected to bind to a wide variety of targets, including receptors on cancer cells
- Their advantages compared to mAbs as targeting ligands is their ease of synthesis, reduced cost, and low immunogenicity



Aptamer

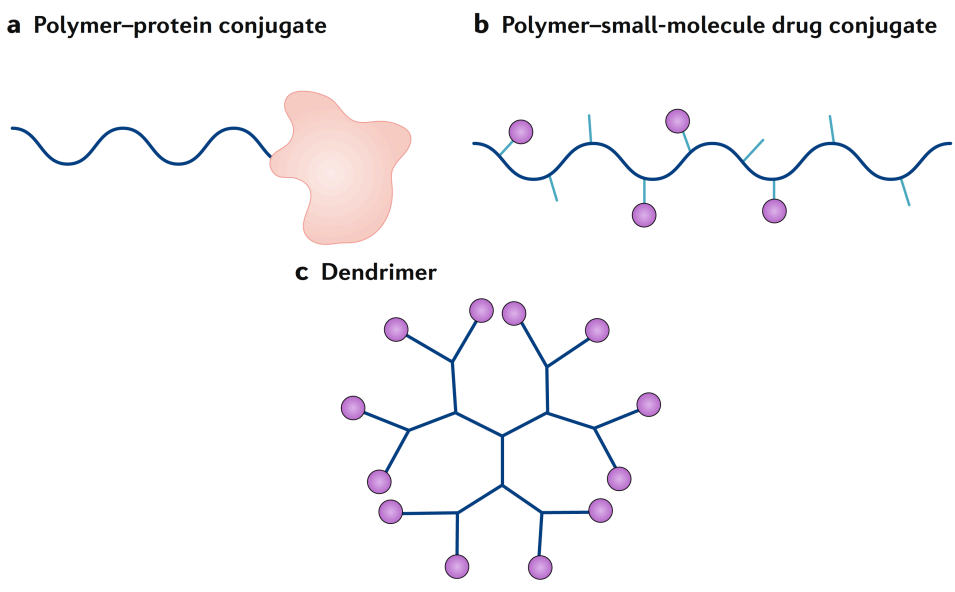
Vitamins and growth factors

- Rationale is that cancer cells often overexpress the receptors for nutrition to maintain their fast-growing metabolism
- e.g. Epidermal growth factor (EGF), folic acid, transferrin
- However, these receptors are also expressed in fast-growing healthy cells, such as fibroblasts, epithelial and endothelial cells
- This could lead to decreased effectiveness and increased toxicity

Polymer-drug conjugates

- One of the first classes of nanocarriers to be approved for clinical use
- PEG (5 kDa – 40 kDa) is the most commonly used
  - FDA-approved
  - Low immunogenicity and toxicity
  - High hydration capacity to improve drug solubility
  - Low polydispersity
  - Ease of modification and conjugation

Polymer-drug conjugates



Polymer-drug conjugates

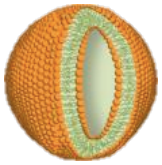
- A linker or spacer is sometimes needed to reduce steric hindrance by the polymer
- The linker can be designed to be cleaved under certain conditions (pH, enzymes, hydrolysis)
- Groups: amide (most common), ester, carbamate
- Drugs used for conjugation are usually anticancer drugs to improve targeting and reduce side effects
- Also protein drugs such as L-asparaginase and interferons to improve their stability and $t_{1/2}$

Some licensed polymer-drug conjugates

Brand name	Polymer-drug	Indication
Oncaspar®	PEG-asparaginase	Acute lymphoblastic leukemia
PEG-Intron®	PEG-interferon 2b	Hepatitis C
Macugen®	PEG-anti VEGF aptamer	Age-related macular degeneration

Liposomes

- Spherical vesicles consisting of an aqueous core surrounded by a phospholipid bilayer



- Unlike micelles which form spontaneously, liposomes require energy to drive their formation
- Capable of carrying hydrophilic molecules (in the core) and lipophilic molecules (in the bilayer)
- Anionic molecules (nucleic acids) can also adsorb on the surface of cationic liposomes

Liposomes

- The first liposomal product to be approved is Doxil® (1995)
- The majority of products are administered IV, some products are used in cosmetics (topical)
- Examples:
  - Doxil®(doxorubicin), DaunoXome® (daunorubicin) -> cancer
  - AmBisome® (amphotericin B) -> systemic fungal infections
  - Inflexal V® -> influenza vaccine

Polymeric nanoparticles

- Submicron-sized polymeric colloidal particles where the drug can be dissolved, entrapped, encapsulated, or conjugated to the surface
- Advantages:
  - Wide range of drugs can be incorporated
  - Controlled release characteristics
  - Ability to deliver proteins, peptides, and genes
  - Enabling targeting to tissues and organs

Polymeric nanoparticles and the EPR effect

- The surface of the nanoparticles can be coated with PEG to produce “stealth” nanoparticles
- This is achieved by employing PEGylated copolymers (e.g. PEG-PLGA, PEG-PCL, …)
- The hydrated PEG layer prohibits protein and antibody binding → reduced recognition and clearance
- This increases plasma circulation of the nanoparticles and allows their accumulation at sites of leaky vasculature like tumors tissues (passive targeting)
- Active targeting can also be achieved by decorating the surface of the nanoparticles with targeting groups

Biodegradable polymeric nanoparticles

- A number of different polymers, both synthetic and natural, have been utilized in formulating biodegradable nanoparticles:
  - Poly(lactide-co-glycolide) (PLGA)
  - Polylactic acid (PLA)
  - Polycaprolactone (PCL)
  - Chitosan
  - Alginate
  - Gelatin

Biodegradable polymeric nanoparticles

- PLGA and PLA have been the most extensively investigated
  - They are polyesters in nature
  - Undergo hydrolysis in the body producing biocompatible moieties (lactic acid and glycolic acid)
- Current uses:
  - Resorbable sutures
  - Bone implants and screws
  - Contraceptive implants
  - As tissue engineering scaffolds

Protein nanoparticles

- Abraxane®: 130 nm particles of albumin-bound paclitaxel
- The older paclitaxel product, Taxol®,contains paclitaxel solubilized in Cremophor® EL (castor oil derivative)
- Taxol® requires special infusion sets, prolonged infusion times, and has toxic side effects
- The Abraxane® formula enhances the drug's solubility without the side effects
- Abraxane® also allows passive targeting by the EPR effect

Drug nanocrystals

- Nanosized particles of pure drug normally formulated as nanosuspensions stabilized with one or more surfactants
- Can also be formulated as tablets or capsules, but high drug loading can lead to crystal fusion during compression
- Therefore, tablet formulations are best suited for low dose drugs

Rapamune®

- The first nanocrystal-based product on the market
- A nanocrystal tablet of sirolimus
- Sirolimus is also available as an oral suspension
- The bioavailability of the nanocrystal tablet is 21% higher compared to the suspension

Hope you enjoyed this course and good luck ☺